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Alcohol enhances acinar cell expression of pro- and anti-inflammatory mediators and pro-fibrotic TGF-β in sub-clinical acute pancreatitis.

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Pancreatitis is an inflammatory disease with potential life-threatening conditions. Mediators, including TNF-α, IL-6, IL-10, MCP-1, inflammasome-associated caspase-1 and IL-18 as well as pro-fibrotic TGF-β, are known to play a critical role in the pathophysiology of pancreatitis. However, the convincible evidences for the origin of these pro- and anti-inflammatory mediators as well as pro-fibrogenic factors in pancreas are still missing. In the present study, we put the emphasis on the role of acinar cells in initiating acute pancreatitis and fibrogenic responses during the early onset of alcoholic acute pancreatitis induced by LPS in a rat model. The potential mechanisms of acinar cells response to endotoxin have been determined as well.

This study shows that acinar cells produce TNF-α, IL-6, MCP-1 and IL-10 as early as 3 hours after the onset of experimental sub-clinical AP and were completely or partially restored to normal level 24 hours later. In addition, the TGF-β and the inflammasome-associated IL-18 and caspase-1 expressions were evident at the late stage (24 hours later. The expression of all these inflammatory mediators were significantly enhanced after endotoxin in acinar cells and the expression were enhanced after alcohol exposure, indicating a synergistic effect of LPS and alcohol on inflammatory response. The blockage of LPS signaling *in vitro* diminished TNF-α production, indicating that pancreatic acinar cells responding to LPS in a way similar to immune cells via TLR-4/NFκB signalling pathway. Furthermore, mild acute pancreatitis can establish peri-acinar cell fibrosis 24 hours after endotoxemia prior to visible tissue necrosis. Similar results were found in human acute/recurrent pancreatitis specimens.

In the present study, we demonstrate that pancreatic acinar cells are the predominantly cell type driving early pancreatic inflammation and fibrosis in the pathogenesis of pancreatitis and response to LPS is similar as reported for human immune cells. Furthermore pancreatic fibrosis, manifested in chronic pancreatitis can be well established in the early phase of acute pancreatitis with no/little necrosis required in our model.